UNIVERSITY OF OKLAHOMA MEDICAL CENTER

IMPROVEMENT OF RENAL HEMODYNAMICS IN ENDOTOXIN SHOCK WITH DOPAMINE, PHENOXYBENZAMINE AND DEXTRAN

Linda L. Shanbour, Robert D. Lindeman, Linda T. Archer,

Su Hsin Tung, and Lerner B. Hinshaw

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Abstract

Linda L. Shanbour, Robert D. Lindeman, Linda T. Archer,

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Improvement of Renal Hemodynamics in Endotoxin Shock

with Dopamine, Phenoxybenzamine and Dextran

The effects of dopamine were evaluated on the renal hemodynamics of dogs in endotoxin shock. In control animals receiving endotoxin only, mean systemic arterial pressure decreased to 60%, renal blood flow decreased to 51%, renal resistance increased to 116%, glomerular filtration rate decreased to 9% and urine flow decreased to 18% of control values. Pre- and post-treatment of shocked animals with dopamine showed no significant improvements in any of the measured parameters. Post-treatment with a combination of phenoxybenzamine (1 mg/kg), dextran (20 cc/kg) and dopamine (mean infusion rate of 38 μg/kg/min) significantly changed the measured parameters in endotoxin injected animals. In this group, mean systemic arterial pressure was 65%, renal blood flow was 128%, renal resistance was 47%, glomerular filtration rate was 29% and urine flow was 117% of control values at the termination of the dopamine infusion. Thirty minutes following termination of the dopamine infusion, mean systemic arterial pressure was 59%, renal blood flow was 69%, renal resistance was 76%, glomerular filtration rate was 19% and urine flow was 44% of control values. These findings show that dopamine significantly improves renal hemodynamics in endotoxin shock only when phenoxybenzamine is given to block the constrictor action of dopamine and when dextran is administered for volume replacement concomitantly with dopamine infusion.

Endotoxin shock can be fatal to clinical subjects if it causes irreversible damage. Even after hemodynamic function has been improved, the patient may die in renal failure. Dopamine (3,4-dihydroxyphenylethylamine) appears to benefit patients in various shock states (MacCannell *et al.*, 1966). In hemorrhagic shock, for example, dopamine improves heart (Carvalho *et al.*, 1969) and kidney (Gifford *et al.*, 1968) function. Studies from this laboratory, using dogs shocked with endotoxin, have shown that dopamine increases venous return independent of a direct effect on the heart (Shanbour and Hinshaw, 1969a); the liver being a primary site of its action. Dopamine produced a marked release of blood both in the normal and shocked isolated liver preparations (Shanbour and Hinshaw, 1969b). Moreover, McDonald *et al.* (1964) reported that dopamine increases the renal plasma flow in normal subjects and patients in heart failure. McNay *et al.* (1965) pointed out the unique ability of dopamine to produce femoral artery constriction and, at the same time, renal vasodilation. Most other agents previously reported to increase renal blood flow also increased femoral blood flow (McNay and Goldberg, 1965). Because beta-adrenergic blocking agents fail to interfere with its renal vasodilating properties (McNay *et al.*, 1963), dopamine probably acts on an undefined receptor in the kidney (Meyer *et al.*, 1967; Goldberg *et al.*, 1968; Yeh *et al.*, 1969). Such a receptor has been suggested to exist (Eble, 1964) in the mesenteric vascular bed of the dog. Dopamine increases urine flow but the increase is not dependent upon systemic hemodynamic changes (Meyer *et al.*, 1967).

Because of the previously described effects of dopamine, studies were conducted to determine its action on renal hemodynamics in the endotoxin-shocked animal.

METHODS. Forty adult mongrel dogs, unselected by age or sex, weighing 7-15 kg, were anesthetized intravenously with sodium pentobarbital, 30 mg/kg. A femoral artery was cannulated for measurements of systemic arterial pressure; Statham pressure transducers monitored the pressures and they were recorded on a Sanborn recorder. The left kidney was exposed through a retroperitoneal flank incision. The renal vein was cannulated and the blood flow was collected in a reservoir placed in a constant temperature water bath (40°C). Renal venous blood was then returned to a femoral vein via a Sigmamotor pump. The renal artery and all nerves supplying it were left intact. Renal blood flow was measured periodically with a stopwatch and graduated cylinder. Glomerular filtration rate was measured by the I^{125} iothalamate clearance method $[(\frac{A-V}{A})\ (RPF)]$. Renal plasma flow was calculated as (renal blood flow) $(\frac{100\text{-hematocrit}}{100})$. Renal resistance was calculated as mean systemic arterial pressure divided by renal blood flow. Hematocrit and pH determinations were made periodically throughout the experiments. In addition, oxygen consumption values were determined in the endotoxin control group. *Escherichia coli* endotoxin was administered i.v. at an LD_{80} level (1.5 mg/kg). Dopamine (California Biochemical Corporation) was dissolved in 0.9% saline to a final concentration of 1 mg/cc; it was administered i.v. at a rate producing maximal increase in renal blood flow (mean infusion rate, 38 µg/kg/min). Phenoxybenzamine (Dibenzyline) was administered in a dose sufficient to block the vasoconstrictor action of dopamine (1 mg/kg). Dextran (20 mg/kg) was given to increase circulating blood volume. For control experiments, 0.9% saline was infused at the same rate as the dopamine-saline combination. The preparation was stable for 30 minutes before any substance was administered. The moment of endotoxin

injection was always recorded as zero time, independent of pre-treatment.

Five main groups of experiments were performed (6 animals in each). In Group A, endotoxin alone was given. Group B dogs received saline infusion, beginning 20 minutes before and continued 120 minutes after endotoxin administration. In Group C, animals were pre-treated with dopamine; infusion of the compound started 20 minutes before endotoxin administration and was continued for 120 minutes after endotoxin. In Group D, dopamine infusion was not begun until a shock state (mean systemic arterial pressure less than 80 mm Hg) was manifest (10-40 minutes after endotoxin injection). Group E dogs were given a combination of agents after endotoxin shock became apparent. At this time, phenoxybenzamine and dextran were administered and a dopamine infusion was started and maintained for 140 minutes.

In Groups A and B, values were recorded at zero time (endotoxin injection) and again at 30, 60 and 120 minutes. In Groups C through E, however, the response of the animal determined the course of the experiment. Control values were always taken just before endotoxin administration, but the studies extended anywhere from 120 to 240 minutes thereafter. Post-endotoxin values were recorded: (1) when the animal reached a shock state; (2) when renal blood flow was at its maximum; (3) at the end of treatment with the agents used; and (4) on termination of the experiment.

Statistical analysis was performed according to the standard "t" test for comparisons between means.

RESULTS. Table 1 presents mean values ± standard errors of the mean for the measured parameters in the five main groups. Statistical comparisons between mean values are shown as $p < 0.10$, $p < 0.05$ and $p < 0.01$.

However, differences were not considered significant unless $p < 0.05$. Since the experiments were designed to approach the clinical situation as closely as possible, treatment was not started until a shock state was manifest. Therefore, grouping of values according to times was impossible and the values presented in Groups C, D and E are those after endotoxin, at maximal renal blood flow, end of treatment and end of study.

Group A (Endotoxin alone): The mean systemic arterial pressure, renal blood flow, glomerular filtration rate, urine flow and pH significantly decreased. However, renal resistance, heart rate, and hematocrit remained relatively stable. In addition, oxygen consumption values showed a decrease after endotoxin administration followed by a recovery towards control values. A typical example of this group is shown in Figures 1 and 2.

Group B (saline infusion before and after endotoxin administration): The animals in this group responded essentially the same as those in Group A.

Group C (dopamine infusion started 20 minutes before and maintained for 120 minutes after endotoxin administration): After endotoxin injection, significant decreases in mean systemic arterial pressure, renal blood flow, glomerular filtration rate and pH were observed. Renal blood flow continued to decline in these experiments. When maximal renal blood flow was achieved following endotoxin administration and during dopamine infusion, there was no significant change in mean systemic arterial pressure; however, there was a significant increase in renal resistance. During the control period, the heart rate accelerated markedly because dopamine was infused before zero time (endotoxin administration). The urine flow rate markedly decreased throughout the experiments. After the infusion was stopped, the pH increased significantly.

Group D (dopamine infusion after endotoxin administration): Mean systemic arterial pressure, renal blood flow, glomerular filtration rate and pH significantly decreased and hematocrit increased following endotoxin administration and prior to treatment. The urine flow showed a marked decrease. However, statistical evaluation was not possible since three out of six of the urine flows were zero after endotoxin and before treatment. When the maximal renal blood flow was reached during the dopamine infusion, there was observed a pressor effect of the dopamine and the renal resistance showed a tendency to increase. Dopamine infusion elicited a significant rise in glomerular filtration rate, followed by a decrease. Urine flow showed a tendency to increase with dopamine infusion. Heart rate accelerated significantly, then slowed after termination of the infusion. As in the Group C experiments, the pH tended to increase when the infusion was stopped. The hematocrit decreased significantly between the end of infusion and termination of the experiment.

Group E (phenoxybenzamine, dextran and dopamine infusion after endotoxin administration): Between endotoxin administration and treatment, significant decreases occurred in mean systemic arterial pressure, renal blood flow, glomerular filtration rate, urine flow, heart rate and pH, accompanied by an increase in the hematocrit. Thereafter, mean systemic arterial pressure remained fairly constant. Renal blood flow improved strikingly (to above control values) until dopamine infusion was stopped, after which it dropped once again. Concomitantly, renal resistance fell until the infusion was stopped; then it tended to rise. Glomerular filtration rate increased with treatment and decreased afterward. Similarly, urine flow increased (to above control levels) and then decreased. Dopamine did not prevent slight decreases in the pH. A typical example of this group is shown in Figure 1 and 2.

DISCUSSION. Although dopamine significantly increases renal blood flow in normal dogs (McNay and Goldberg, 1965), when administered alone in endotoxin shock, no significant benefits are apparent. Dopamine alone seems, at best, to improve renal function only temporarily, regardless of the duration or rate of infusion. This is true whether the dopamine is administered as pre- or post-treatment. The typical chronotropic action of dopamine on the heart was observed. Since dopamine infusion never significantly improved renal blood flow, the adrenergic blocking agent phenoxybenzamine (Dibenzyline) was administered at a level just sufficient to block any vasoconstriction as tested by prior injections of epinephrine. Since phenoxybenzamine would tend to lower an already low circulating blood volume, dextran was administered for volume replacement. There are conflicting reports in the literature concerning the effectiveness of phenoxybenzamine alone and in combination with dextran in endotoxin shock treatment. Some investigators have reported that pretreatment of endotoxin shock with phenoxybenzamine increased survival rate in dogs and mice (Lillehei and MacLean, 1958; Lillehei *et al.*, 1964; Gourzis *et al.*, 1961). Others have reported opposite results (Weil and Allen, 1964; Masucci and Hinshaw, 1964). Similar conflicting results are reported for post-treatment with phenoxybenzamine (Vick, 1964; Weil and Allen, 1964; Weil and Miller, 1961; Nickerson and Carter, 1959). Pre- and post-treatment with a combination of phenoxybenzamine and dextran has been reported to not mitigate the lethal effects of endotoxin (Masucci *et al.*, 1966). Dextran is reported to increase survival rate in hemorrhagic (Pirani *et al.*, 1955) but not in tourniquet shock (Serkes *et al.*, 1959). Dopamine is unique in that its

vasodilating action is not blocked by beta-adrenergic blocking agents (McNay *et al.*, 1963) and it (differentially) constricts the femoral bed while dilating the renal bed and, therefore, probably acts directly on the kidney (McNay *et al.*, 1965). Although this effect is easily seen in normal animals, we were never able to increase the renal blood flow to control levels in the shocked animal. It is therefore of interest that post-treatment of endotoxin shock with phenoxybenzamine, dextran and dopamine increased renal blood flow and urine flow to above control values. These recovery values, along with the observation that the renal oxygen consumption values decrease following endotoxin administration but then show recovery towards control values, suggest that endotoxin does not have a direct toxic effect on the kidney. The multiple-treatment decreased the hematocrit rise due to endotoxin injection. This is consistent with the finding that pre-treatment with phenoxybenzamine produces comparable hematocrit results (Lillehei and MacLean, 1959). The multiple treatment did not correct the acidosis due to endotoxin injection. The agents administered alone or in all possible combinations of two did not produce the salutary effects of the triple combination. This is consistent with the above mentioned findings.

Although dopamine itself does not significantly improve renal hemodynamics and function in dogs in endotoxin shock, an effective therapy would appear to be a combination of dopamine, phenoxybenzamine and dextran.

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LEGENDS FOR FIGURES

Figure 1. Mean systemic arterial pressure, renal blood flow and renal resistance in typical control and multiple-treatment experiments. The dotted line represents endotoxin alone; the solid line represents endotoxin followed by triple treatment.

Figure 2. Glomerular filtration rate and urine flow in typical control and multiple-treatment experiments. The dotted line represents endotoxin alone; the solid line represents endotoxin followed by triple treatment.

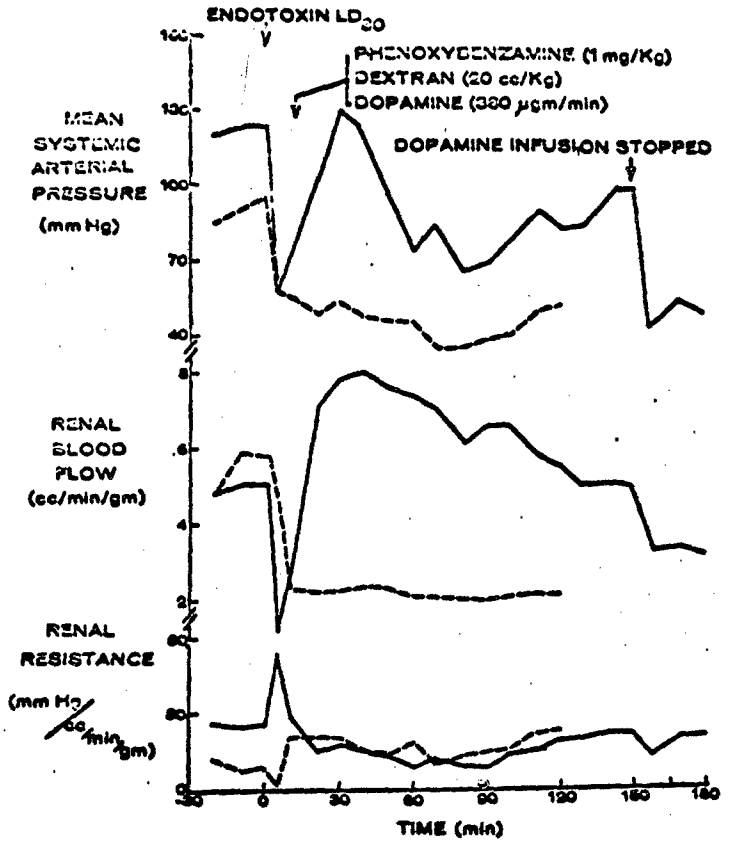
ENDOTOXIN LD20
PHENOXYBENZAMINE (1 mg/Kg)
DEXTRAN (20 cc/Kg)
DOPAMINE (300 µgm/min)
DOPAMINE INFUSION STOPPED
MEAN SYSTEMIC ARTERIAL PRESSURE (mm Hg)
RENAL BLOOD FLOW (cc/min/gm)
RENAL RESISTANCE
(mm Hg / cc/min/gm)
TIME (min)

FIGURE I

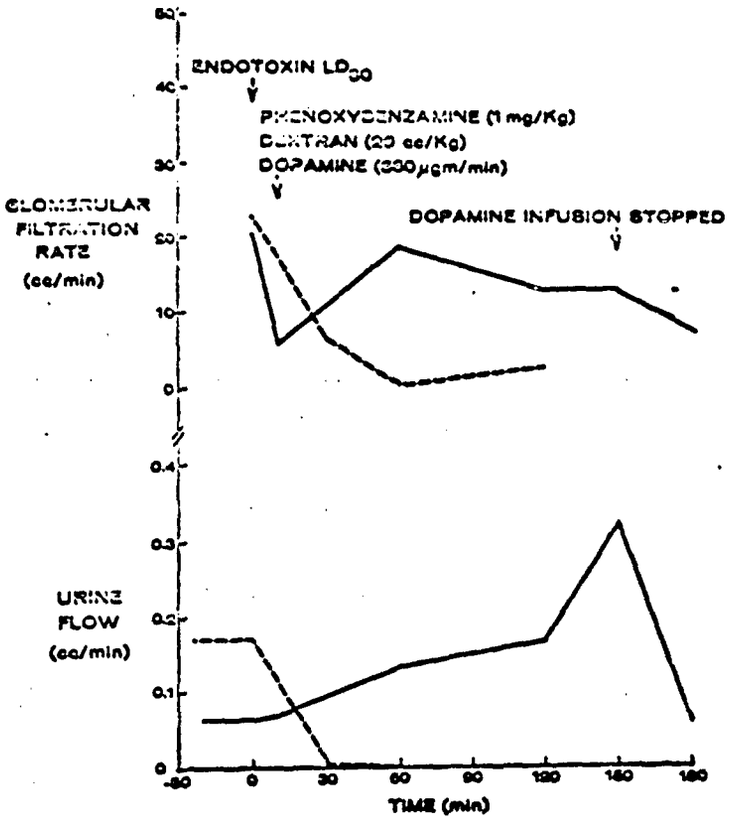
ENDOTOXIN LD50
PHENOXYBENZAMINE (1 mg/Kg)
DEXTRAN (20 cc/Kg)
DOPAMINE (300μgm/min)
DOPAMINE INFUSION STOPPED
GLOMERULAR FILTRATION RATE (cc/min)
URINE FLOW (cc/min)
TIME (min)

FIGURE 2

Table 1. Control and Treated Endotoxin-Shocked Groups

Time	Mean Systemic Arterial Pressure (mm Hg)	Renal Blood Flow (cc/min/gm)	Renal Resistance (mm Hg/cc/min/gm)	Glomerular Filtration Rate (cc/min)	Urine Flow (cc/min)	Heart Rate (beats/min)	pH (Arterial)	Hct (%)
			A. ENDOTOXIN ONLY (6 ANIMALS)					
0	113 ± 7	4.7 ± 0.4	25 ± 3	21.7 ± 1.3	0.45 ± 0.25	145 ± 11	7.32 ± 0.03	34 ± 2
+30	81 ± 11***	3.8 ± 0.6***	22 ± 2	12.1 ± 2.8**	0.07 ± 0.02***	132 ± 10	7.23 ± 0.04***	35 ± 4
+60	57 ± 8***	2.6 ± 0.4***	23 ± 2	1.2 ± 1.5***	0.05 ± 0.05***	152 ± 13	7.25 ± 0.05***	35 ± 3
+120	67 ± 5***	2.4 ± 0.2***	29 ± 4	2.0 ± 1.2***	0.08 ± 0.03***	157 ± 12	7.25 ± 0.04*	35 ± 3
			B. SALINE PRE-ENDOTOXIN (6 ANIMALS)					
0	118 ± 5	4.0 ± 0.2	30 ± 2	20.8 ± 2.2	0.24 ± 0.01	140 ± 14	7.27 ± 0.05	35 ± 2
+30	78 ± 2***	2.7 ± 0.1***	29 ± 2	13.5 ± 1.5*	0.11 ± 0.05**	125 ± 14	7.13 ± 0.02***	33 ± 2
+60	58 ± 6***	2.3 ± 0.2***	26 ± 2*	6.4 ± 1.7**	0.02 ± 0.02***	130 ± 13	7.19 ± 0.04**	39 ± 4
+120	66 ± 3***	2.0 ± 0.3***	33 ± 1	3.5 ± 1.4**	0***	145 ± 14	7.23 ± 0.07	37 ± 3
			C. DOPAMINE PRE-ENDOTOXIN (6 ANIMALS)					
Control	120 ± 9	4.7 ± 0.5	27 ± 3	19.0 ± 5.1	0.21 ± 0.08	197 ± 10	7.20 ± 0.03	35 ± 2
After Endotoxin	91 ± 10**	3.9 ± 0.6*	25 ± 2	8.1 ± 5.2*	0.09 ± 0.07	207 ± 19	7.16 ± 0.05*	33 ± 3
Value at Max. RBF	108 ± 8	3.3 ± 0.5*	37 ± 7*	-	-	-	-	-
End of Treatment	85 ± 10	1.7 ± 0.5	75 ± 35	5.6 ± 3.2	0.05 ± 0.03	183 ± 19**	7.12 ± 0.03	28 ± 3*
End of Study	56 ± 11	1.7 ± 0.8	328 ± 186	4.0 ± 3.8	0.02 ± 0.02	161 ± 14*	7.23 ± 0.03**	29 ± 2
			D. DOPAMINE POST-ENDOTOXIN (6 ANIMALS)					
Control	121 ± 8	4.3 ± 0.5	30 ± 3	29.0 ± 5.2	0.31 ± 0.09	161 ± 14	7.37 ± 0.03	38 ± 2
After Endotoxin	67 ± 4***	2.3 ± 0.4**	33 ± 6	1.4 0.8***	0.03 ± 0.01	151 ± 7	7.28 ± 0.02*	44 ± 3**
Value at Max. RBF	92 ± 11**	3.0 ± 0.3	32 ± 2	7.0 ± 3.1**	0.13 ± 0.03	249 ± 12***	7.24 ± 0.02	44 ± 4
End of Treatment	78 ± 7	2.3 ± 0.3	39 ± 9	5.7 ± 2.8	0.01 ± 0.004	217 ± 23	7.23 ± 0.04	43 ± 4
End of Study	66 ± 4	1.6 ± 0.3*	56 ± 22	3.3 ± 1.7	0.06 ± 0.04	136 ± 30**	7.32 ± 0.05	39 ± 4**
			E. MULTIPLE-TREATMENT (6 ANIMALS)					
Control	129 ± 7	3.6 ± 0.3	38 ± 5	20.6 ± 1.8	0.18 ± 0.04	150 ± 13	7.35 ± 0.03	32 ± 5
After Endotoxin	75 ± 10***	2.2 ± 0.5*	43 ± 12	5.0 ± 3.4**	0.10 ± 0.03*	123 ± 9**	7.29 ± 0.03***	38 ± 4**
Value at Max. RBF	89 ± 9	5.6 ± 0.9**	17 ± 2*	9.3 ± 4.2*	0.11 ± 0.06	215 ± 22***	7.29 ± 0.02	38 ± 1
End of Treatment	84 ± 7	4.6 ± 0.3	18 ± 1	5.9 ± 2.3	0.21 ± 0.09	190 ± 30	7.27 ± 0.06	33 ± 3
End of Study	76 ± 11	2.5 ± 0.4***	29 ± 8	4.0 ± 1.8	0.08 ± 0.01	147 ± 16***	7.23 ± 0.08	31 ± 3

± = Standard Error of the Mean
* = $p<0.10$ (showing a tendency)
** = $p<0.05$ (considered as significant)
*** = $p<0.01$ (considered as very significant)

Values in Groups A and B are compared with control (zero) values.
Statistical comparisons in Groups C, D and E are between:
control and after endotoxin.
after endotoxin and value at maximal renal blood flow.
end of treatment and end of study.

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13. ABSTRACT

The effects of dopamine were evaluated on the renal hemodynamics of dogs in endotoxin shock. In control animals receiving endotoxin only, mean systemic arterial pressure decreased to 60%, renal blood flow decreased to 51%, renal resistance increased to 116%, glomerular filtration rate decreased to 9% and urine flow decreased to 18% of control values. Pre- and post-treatment of shocked animals with dopamine showed no significant improvements in any of the measured parameters. Post-treatment with a combination of phenoxybenzamine (1 mg/kg), dextran (20 cc/kg) and dopamine (mean infusion rate of 38 µg/kg/min) significantly changed the measured parameters in endotoxin injected animals. In this group, mean systemic arterial pressure was 65%, renal blood flow was 128%, renal resistance was 47%, glomerular filtration rate was 29% and urine flow was 117% of control values at the termination of the dopamine infusion. Thirty minutes following termination of the dopamine infusion, mean systemic arterial pressure was 59%, renal blood flow was 69%, renal resistance was 76%, glomerular filtration rate was 19% and urine flow was 44% of control values. These findings show that dopamine significantly improves renal hemodynamics in endotoxin shock only when phenoxybenzamine is given to block the constrictor action of dopamine and when dextran is administered for volume replacement concomitantly with dopamine infusion.

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